Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 9, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.02.002

SCANNING THE LITERATURE

# Summaries of Key Journal Articles

Kim A. Eagle, MD, FACC, Editor-in-Chief, Journal Scan, *Ann Arbor, MI*

Christopher P. Cannon, MD, FACC, Editor-in-Chief, Cardiosource, *Boston, MA*

William F. Armstrong MD, FACC, *Ann Arbor, MI*, David S. Bach, MD, FACC, *Ann Arbor, MI*, Ragavendra R. Baliga, MBBS, FACC, *Columbus, OH*, Timothy B. Cotts, MD, FACC, *Ann Arbor, MI*, Daniel T. Eitzman, MD, FACC, *Ann Arbor, MI*, James B. Froehlich, MD, FACC, *Ann Arbor, MI*, Caren S. Goldberg, MD, FACC, *Ann Arbor, MI*, Hitinder S. Gurm, MBBS, FACC, *Ann Arbor, MI*, Jennifer C. Hirsch, MD, FACC, *Ann Arbor, MI*, Elizabeth Anne Jackson, MD, FACC, *Ann Arbor, MI*, Fred Morady, MD, FACC, *Ann Arbor, MI*, Debabrata Mukherjee, MD, FACC, *Lexington, KY*, Himanshu J. Patel, MD, FACC, *Ann Arbor, MI*, Melvyn Rubenfire, MD, FACC, *Ann Arbor, MI*, Gilbert R. Upchurch, Jr., MD, *Ann Arbor, MI*, Associate Editors, Cardiosource

## Arrhythmias

### Vasopressin, Epinephrine, and Corticosteroids for In-Hospital Cardiac Arrest

**Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al.**
***Arch Intern Med* 2009;169:15-24.**

**Study Design:** Does the combination of epinephrine, vasopressin, and methylprednisolone improve survival compared to epinephrine alone in patients with in-hospital cardiac arrest (IHCA)?

**Methods:** One hundred patients with IHCA were randomly assigned to receive 1 mg of epinephrine (control group, n = 52) during five cycles of cardiopulmonary resuscitation (CPR) or the combination of 1 mg of epinephrine and 20 IU of vasopressin during the first five CPR cycles and 40 mg of methylprednisolone during the first cycle, followed by 300 mg/day of hydrocortisone for up to 7 days (study group, n = 48).

**Results:** Return of spontaneous circulation was significantly higher in the study group (81%) than in the control group (52%). Survival to hospital discharge also was significantly higher in the study group (19%) than in the control group (4%).

**Conclusions:** Compared to epinephrine alone, the combination of vasopressin, epinephrine, and corticosteroids improves survival after IHCA.

**Perspective:** In a much larger randomized trial that included nearly 2,900 patients with out-of-hospital cardiac arrest (*N Engl J Med* 2008;359:21-30), combination therapy with epinephrine plus vasopressin did not improve outcomes compared to epinephrine alone. This suggests that the improved survival in the present study group was more a result of therapy with corticosteroids than vasopressin. Corticosteroids may exert the following beneficial effects during and after CPR: improvement in contractile function during and after ischemia, increase in peripheral arterial tone, decrease in systemic inflammatory response, and attenuation of post-CPR adrenal insufficiency.

*Summary written by: Fred Morady, MD, FACC*

### Large Scale Replication and Meta-Analysis of Variants on Chromosome 4q25 Associated With Atrial Fibrillation

**Kääb S, Darbar D, van Noord C, et al.**
***Eur Heart J* 2009;Jan 13:[Epub ahead of print].**

**Study Design:** Is the association between genetic variation on chromosome 4q25 and atrial fibrillation (AF) reproducible when applied to other cohorts?

**Methods:** This association was analyzed in four independent cohorts, including 12,173 patients. The Framingham Heart Study and Rotterdam Study are community-based longitudinal studies. The Vanderbilt AF Registry and German AF Network (AFNet) are case-control studies.

JACC Vol. 53, No. 9, 2009
March 3, 2009:817–24

**Results:** Participants with AF (n = 3,508) were more likely to be male and were older than referent participants. Single nucleotide polymorphism (SNP) rs2200733 was associated with AF in all four cohorts, with odds ratios (ORs) ranging from 1.37 in Rotterdam (95% confidence interval [CI], 1.18-1.59; p = 3.1 x 10-5) to 2.52 in AFNet (95% CI, 2.22-2.8; p = 1.8 x 10-49). There also was a significant association between AF and rs10033464 in Framingham (OR, 1.34; 95% CI, 1.03-1.75; p = 0.031) and AFNet (OR, 1.30; 95% CI, 1.13-1.51; p = 0.0002), but not Vanderbilt (OR, 1.16; 95% CI, 0.86-1.56; p = 0.33).

**Conclusions:** The noncoding SNPs rs2200733 and rs10033464 are strongly associated with AF in four cohorts of European descent.

**Perspective:** While hypertension and valvular heart disease are important risk factors for AF, other independent genetic factors have been shown to be associated with AF. A recent genome-wide association study identified a haplotype block on chromosome 4q25 associated with AF. The SNPs that define this haplotype block are located in a noncoding region of the genome. The current study provides strong additional support for the association of AF with genetic variation at this region. The underlying mechanism for this genetic association remains elusive, although the closest gene (transcription factor PITX2) is an attractive candidate.

*Summary written by: Daniel T. Eitzman, MD, FACC*

# Cardiovascular Surgery

## Sex Differences in Hospital Risk-Adjusted Mortality Rates for Medicare Beneficiaries Undergoing CABG Surgery

**Culler SD, Simon AW, Brown PP, Kugelmass AD, Reynolds MR, Rask KJ.**
***Arch Intern Med* 2008;168:2317-2322.**

**Study Question:** What are the overall and sex-specific differences after coronary artery bypass graft surgery (CABG) on Medicare beneficiaries in the risk-adjusted mortality rates across four performance tiers?

**Methods:** A retrospective analysis was done using a Medicare Provider Analysis and Review file of all Medicare beneficiaries who underwent CABG during 2003 and 2004. Logistic regression models controlling for demographics, comorbidities, and cardiac risk factors were used to predict the probability of in-hospital mortality. Hospitals performing at least 52 CABG surgeries during a fiscal year (at least 17 female patients) were ranked into four tiers, based on the number of lives saved.

**Results:** Average risk-adjusted mortality rate was stable and declining over the 2 years: 3.68% in 2003 and 3.61% in 2004. In 2004, the average risk-adjusted mortality rate ranged from 1.39% in tier 1 hospitals to 6.40% in tier 4 hospitals. The sex-specific mortality rate was consistently higher for women in all tiers, with the differential smallest (0.68%) in tier 1 hospitals and greatest (2.67%) in tier 4 hospitals.

**Conclusions:** The sex differential increases from top- to bottom-tier hospitals, suggesting female beneficiaries could benefit from having CABG performed at tier 1 hospitals.

**Perspective:** This study suggests that Medicare beneficiaries should pay close attention to hospital performance rankings for CABG based on lives saved. Improving the quality of care in poorer-performing hospitals may improve CABG outcomes. The difference in average risk-adjusted mortality rates across hospital tiers is substantially larger than the overall reduction in CABG mortality that has been achieved over the last decade with clinical advances in performing the procedure. Future research is needed to focus on the processes and structures that differentiate the top performing hospitals from the bottom performers, and how this knowledge can be translated to other hospitals.

*Summary written by: Debabrata Mukherjee, MD, FACC*

# Congenital Heart Disease

## Association Between Intraoperative and Early Postoperative Glucose Levels and Adverse Outcomes After Complex Congenital Heart Surgery

**Polito A, Thiagarajan RR, Laussen PC, et al.**
***Circulation* 2008;118:2235-2242.**

**Study Question:** What associations exist between perioperative glucose exposure and morbidity after complex congenital heart surgery?

**Methods:** Patients at a single center undergoing cardiac surgery with a Risk Adjustment in Congenital Heart Surgery (RACHS-1) category ≥3 over a 1-year period were included (n = 378). Metrics of glucose control, including average, peak, minimum, and SD of glucose levels were studied. Multiple regression analyses were used to determine associations between glucose control and both length of hospital stay and a composite outcome of morbidity and mortality.

**Results:** For intraoperative glucose levels, only a minimum glucose of ≤75 mg/dl was associated with increased risk of reaching the composite endpoint (odds ratio, 3.1; 95% confidence interval, 1.49-6.48). Only duration of hyperglycemia

(glucose >126 mg/dl) was associated with longer duration of hospitalization ($p < 0.001$). For the first 72 hours after surgery, average glucose <110 mg/dl, or >143 mg/dl, minimum glucose ≤75 mg/dl, and peak glucose ≥250 mg/dl were all associated with greater odds of reaching the composite morbidity-mortality endpoint.

**Conclusions:** The optimal postoperative glucose range may be from 110-126 mg/dl. Further prospective study is warranted.

**Perspective:** The primary limitation of this study is its retrospective design, which precludes any assumptions of causality. While patients with lower blood glucose had poorer outcomes, this may have been reflective of their inability to generate an appropriate stress response. Conversely, elevated postoperative blood glucose may have been reflective of patients who were more ill in the postoperative period. Although this study provides information regarding outcomes of children with various glucose values postoperatively, it cannot be used to demonstrate efficacy of tight glycemic control or the optimal range for blood glucose postoperatively.

*Summary written by: Timothy B. Cotts, MD, FACC*

# General Cardiology

## Cytochrome P-450 Polymorphisms and Response to Clopidogrel

**Mega JL, Close SL, Wiviott SD, et al.**
***N Engl J Med* 2008;360:354-362.**

**Study Question:** What is the clinical impact of polymorphism of cytochrome P-450 among patients treated with clopidogrel?

**Methods:** The association between functional genetic variants in cytochrome P-450 genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel was tested in 162 healthy subjects. The association between these variants and clinical outcomes was evaluated in 1,477 patients with acute coronary syndromes (ACS) who were treated with clopidogrel in the TRITON–TIMI 38 trial.

**Results:** Thirty-four percent of the healthy volunteers were carriers of at least one CYP2C19 reduced-function allele, and this cohort had lower levels of active metabolite and a 25% relative (9% absolute) reduction in maximal platelet aggregation in response to clopidogrel compared with noncarriers ($p < 0.001$). Among the TRITON-TIMI subgroup, 27% of the patients were carriers of the low function allele. The primary composite endpoint (risk of death from cardiovascular causes, myocardial infarction, or stroke) was significantly more common in the carriers (12.1% vs. 8.0%; hazard ratio [HR], 1.53; 95% confidence interval [CI], 1.07-2.19; $p = 0.01$). Carriers were also more likely to develop stent thrombosis (2.6% vs. 0.8%; HR, 3.09; 95% CI, 1.19-8.00; $p = 0.02$).

**Conclusions:** Among persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had lower platelet inhibition in response to clopidogrel and were more likely to suffer adverse ischemic events.

**Perspective:** This landmark paper is likely to change clinical management of patients with ACS. While prasugrel was superior to clopidogrel in the TRITON–TIMI 38 trials, the difference is probably mediated by poor bioavailability of clopidogrel in some patients. The risk of morbid events in patients who were not carriers of the reduced function allele was low and similar to the risk in the overall prasugrel-treated arm. It would be helpful to assess the outcome of a similar cohort randomized to prasugrel to see if the benefit is restricted to carriers of the reduced function allele. I envision a future where genetic screen for the polymorphism is part of the routine clinical care, with clopidogrel being used in 70% of the noncarriers of the allele and prasugrel being used in the remainder.

*Summary written by: Hitinder S. Gurm, MBBS, FACC*

## Glucose Control and Vascular Complications in Veterans With Type 2 Diabetes

**Duckworth W, Abraira C, Moritz T, et al., on behalf of the VADT Investigators.**
***N Engl J Med* 2009;360:129-139.**

**Study Question:** What are the effects of intensive glucose control on cardiovascular events in patients with long-standing type 2 diabetes mellitus?

**Methods:** The investigators randomly assigned 1,791 military veterans who had a suboptimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. Mean number of years since the diagnosis of diabetes was 11.5, and 40% of the patients had already had a cardiovascular event. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level compared with the standard-therapy group. The primary outcome was time from randomization to the first occurrence of a major cardiovascular event.

**Results:** Median follow-up was 5.6 years. Median glycated hemoglobin levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. The primary outcome occurred in 264 standard-therapy and 235 intensive-

JACC Vol. 53, No. 9, 2009
March 3, 2009:817–24

therapy patients (hazard ratio [HR] in the intensive-therapy group, 0.88; 95% confidence interval [CI], 0.74-1.05; p = 0.14). There was no significant difference between the groups in any component of the primary outcome or rate of death from any cause (HR, 1.07; 95% CI, 0.81-1.42; p = 0.62). No differences between the two groups were observed for microvascular complications. The rates of adverse events, predominantly hypoglycemia, were 17.6% in the standard-therapy and 24.1% in the intensive-therapy group.

**Conclusions:** Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications.

**Perspective:** This study, along with the ADVANCE and ACCORD studies, examined intensive glucose control in different populations with different approaches and came to similar conclusions that intensive glucose control did not reduce cardiovascular events in patients with type 2 diabetes. Data suggest that intensive glycemic control earlier in the disease course may potentially produce benefit, especially if severe hypoglycemia is avoided. Optimal management of hypertension, dyslipidemia, and other cardiovascular risk factors appears to be the most effective approach to preventing cardiovascular morbidity and mortality in patients with type 2 diabetes.

*Summary written by: Debabrata Mukherjee, MD, FACC*

## Cytochrome P450 2C19 Polymorphism in Young Patients Treated With Clopidogrel After Myocardial Infarction: A Cohort Study

**Collet JP, Hulot JS, Pena A, et al.**
***Lancet* 2009;373:309-317.**

**Study Question:** What is the clinical impact of the CYP2C19*2 polymorphism of cytochrome P450 2C19 (CYP2C19)?

**Methods:** The authors investigated the outcome of 259 young patients (ages <45 years) who survived a first myocardial infarction (MI) and were treated with clopidogrel for at least a month. All patients underwent CYP2C19*2 determination. The primary endpoint was a composite of death, MI, and urgent coronary revascularization occurring during exposure to clopidogrel. Follow-up was every 6 months. The secondary endpoint was angiographically proven stent thrombosis.

**Results:** Most of the patients were noncarriers (n = 186), whereas 64 were heterozygous (*1/*2), and 9 were homozygous (*2/*2) (n = 9) for the CYP2C19*2 variant. There was no difference in the baseline characteristics between the carriers and noncarriers. The composite primary endpoint occurred more frequently in carriers than in noncarriers (15 vs. 11 events; hazard ratio [HR], 3.69; 95% confidence interval [CI], 1.69-8.05; p = 0.0005). Carriers had higher event rates (per 100 person-years) for cardiovascular death (1.45 vs. 0.26, p = 0.1) and MI (7.27 vs. 1.58, p = 0.001). Carriers were more likely to develop stent thrombosis (6.79 vs. 1.14 events per 1,000 patient-years; HR, 6.02; 95% CI, 1.81-20.04; p = 0.0009).

**Conclusions:** The CYP2C19*2 genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after MI.

**Perspective:** This is the first key publication demonstrating the clinical impact and genetic basis of clopidogrel resistance. Recent studies have demonstrated that inadequate response to clopidogrel is mainly secondary to low plasma levels of clopidogrel metabolite (*J Am Coll Cardiol* 2008;52:1968-77). Polymorphisms of CYP2C19 (*Blood* 2006;108:2244-7) are associated with a marked decrease in platelet inhibition in response to clopidogrel, and this is likely related to inadequate generation of the active metabolite. Results of this study corroborate the high incidence of MI and death in CYP2C19*2 carriers seen in other studies (*J Am Coll Cardiol* 2008;51:1925-34), and suggest that we are likely on the threshold of gene-guided antiplatelet therapy.

*Summary written by: Hitinder S. Gurm, MBBS, FACC*

## Cardiovascular Disease Risk Prediction With and Without Knowledge of Genetic Variation at Chromosome 9p21.3

**Paynter NP, Chasman DI, Buring JE, Shiffman D, Cook NR, Ridker PM.**
***Ann Intern Med* 2009;150:65-72.**

**Study Question:** Does knowledge of 9p21.3 gene variation improve cardiovascular risk prediction over traditional clinical risk factors?

**Methods:** Subjects were 22,129 female white health professionals without major chronic disease and participating in the Women's Genome Health Study, prospectively followed over a median of 10.2 years for incident cardiovascular disease (CVD). Polymorphism at rs10757274 on chromosome 9p21.3, along with additional CVD risk factors, were analyzed.

**Results:** Polymorphism at rs10757274 was associated with an adjusted hazard ratio for incident cardiovascular disease of 1.25 (95% confidence interval [CI], 1.04-1.51) for the AG genotype and 1.32 (CI, 1.07-1.63) for the GG genotype. However, the addition of the genotype to a prediction model based on traditional risk factors, hs-CRP, and family history of premature MI had no effect on model discrimination, and

did not improve the Net Reclassification Improvement score (-0.2%; p = 0.59) or the Integrated Discrimination Improvement score (0.0; p = 0.18).

**Conclusions:** Genetic variation in chromosome 9p21.3 was associated with incident cardiovascular disease, but did not improve on the discrimination or classification of predicted risk achieved with traditional risk factors, hs-CRP, and family history of premature MI.

**Perspective:** Genetic variation at chromosome 9p21.3 is associated with incident CVD; however, it has been unclear whether screening for this polymorphism would improve risk prediction. The current study demonstrates that there is no clinical utility in determining 9p21.3 gene variant status in white women at this time. Although knowledge of novel gene variants may eventually lead to valuable insight into the pathophysiology of complex diseases and new therapeutic targets, the current clinical usefulness of this information remains uncertain.

*Summary written by: Daniel T. Eitzman, MD, FACC*

# Heart Failure/Transplant

## A Meta-Analysis of Randomized Controlled Trials in Pulmonary Arterial Hypertension

**Galiè N, Manes A, Negro L, Palazzini M, Bacchi Reggiani ML, Branzi A.**
***Eur Heart J* 2009;Jan 20:[Epub ahead of print].**

**Study Question:** Does treatment with pulmonary arterial hypertension (PAH)-specific drugs improve survival?

**Methods:** The authors performed a meta-analysis of all randomized, placebo-controlled trials with PAH-specific drugs available in the Medline database from January 1990 to October 2008, including only studies with a placebo comparator arm. The sensitivity analysis also included studies comparing two active treatment arms. The main outcome measure was all-cause mortality.

**Results:** Twenty-one trials were included in the primary analysis (3,140 patients) and two additional studies (59 patients) were included in the sensitivity analysis. The cumulative relative risk (RR) estimate of hospitalizations was a reduction of 61% (p < 0.001), and number needed to treat to prevent one hospitalization was 19.9. Average increase in 6-minute walk distance (6MWD) was 35.6 m or about 10.8% when compared to baseline values. All-cause mortality in the control group was 3.8%. Active treatments were associated with a reduction in mortality of 43% (RR, 0.57; 95% confidence interval [CI], 0.35-0.92; p = 0.023); the sensitivity analysis confirmed a reduction in mortality of 38% (RR, 0.62; 95% CI, 0.39-1.00; p = 0.048).

**Conclusions:** The results of this meta-analysis suggest an improvement of survival in the patients treated with the targeted therapies approved for PAH.

**Perspective:** This meta-analysis includes several entirely different drug classes and trials with the heterogeneity of PAH (e.g., idiopathic, scleroderma, congenital, etc.). Despite that limitation, it provides evidence of a major survival benefit at a mean of 14.3 weeks, in part because of the 1.1% per month mortality in the control group, most of whom are World Health Organization (WHO) class IV with right heart failure. Subgroup analysis according to the different classes of drugs or with baseline exercise capacity, as assessed by 6MWD, did not show statistically significant heterogeneity in the effects on mortality. The authors suggest that the results have not been driven by one class of drugs or by a group of patients with a specific disease severity. That is not consistent with clinical experience in which mortality is highly related to functional class, right heart failure, and specific associated diseases.

*Summary written by: Melvyn Rubenfire, MD, FACC*

## Early and Long-Term Outcomes of Heart Failure in Elderly Persons, 2001-2005

**Curtis LH, Greiner MA, Hammill BG, et al.**
***Arch Intern Med* 2008;168:2481-2488.**

**Study Question:** Are the improvements in heart failure (HF) management reflected in trends in early and long-term mortality and hospital readmission?

**Methods:** This was a retrospective cohort study of 2,540,838 elderly Medicare beneficiaries hospitalized with HF between 2001 and 2005. Early and long-term all-cause mortality and hospital readmission and patient- and hospital-level predictors of these outcomes were examined.

**Results:** Unadjusted in-hospital mortality declined from 5.1% to 4.2% during the study (p < 0.001), but 30-day, 180-day, and 1-year all-cause mortality remained fairly constant at 11%, 26%, and 37%, respectively. Nearly one in four patients were readmitted within 30 days of the index hospitalization, and two-thirds were readmitted within 1 year. Controlling for patient- and hospital-level covariates, the hazard of all-cause mortality at 1 year was slightly lower in 2005 than in 2001 (hazard ratio, 0.98; 95% confidence interval, 0.97-0.99), and the hazard of readmission did not decline significantly.

**Conclusions:** Early and long-term all-cause mortality and hospital readmission rates remain high and have improved little

JACC Vol. 53, No. 9, 2009
March 3, 2009:817–24

with time. The need to identify optimal management strategies for these clinically complex patients is urgent.

**Perspective:** The study findings need to be interpreted in the context that currently management of elderly HF patients is not optimal. The importance of 'core-measures' medications (e.g., angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone blockade) for HF patients is one small step in improving therapy in elderly HF patients. Bridging the gap between evidence and practice should continue to be the key goal of the practicing clinician to improve therapy in the elderly with HF.

*Summary written by: Ragavendra R. Baliga, MBBS, FACC*

# Interventional Cardiology

## Gender Differences Among Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR)

**Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A.**
***Am Heart J* 2009;157:141-148.**

**Study Question:** Do gender-related differences continue to exist, as related to the management and outcomes of patients with acute coronary syndromes (ACS)?

**Methods:** Patients admitted with ACS (unstable angina [UA]/non–ST-elevation myocardial infarction [NSTEMI] or STEMI) and who received a percutaneous coronary intervention (PCI), and were included in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) database from January 1, 2004 to March 30, 2006, were included in this study.

**Results:** A total of 199,690 patients were included in the cohort; 131,664 were men and 68,026 were women. Women were more likely to present with UA or NSTEMI compared to men (82% vs. 77%, $p < 0.001$). Women were more likely to be older and have more comorbidities. Women were less likely to have smoked or to have had prior PCI/coronary artery bypass grafting. Women in both ACS categories had less high-risk angiographic features compared to men, but women with STEMI were more likely to have had cardiogenic shock or nondialysis-dependent renal failure. Women were less likely to receive aspirin or glycoprotein IIb/IIIa inhibitors, and were less likely to receive aspirin or statins at time of discharge. Similar rates of in-hospital mortality were observed for women and men; however, women had higher rates of cardiogenic shock, congestive heart failure, bleeding events, or vascular complications. Rates of subacute stent thrombosis were less among women compared to men (0.43% vs. 0.57%, $p = 0.0003$).

**Conclusions:** Women, despite having fewer high-risk angiographic complications, continue to have higher rates of in-hospital complications. Examining methods for modifying in-hospital management of female ACS patients may reduce post-PCI complications.

**Perspective:** These findings suggest the need for further examination of ACS management in women. Reducing periprocedural complications will assist in improving long-term outcomes for women with heart disease.

*Summary written by: Elizabeth A. Jackson, MD, FACC*

## The Use of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention in Patients With Renal Impairment: Results From the SafeTy and Efficacy of Enoxaparin in PCI Patients, An InternationaL Randomized Evaluation (STEEPLE) Trial

**White HD, Gallo R, Cohen M, et al.**
***Am Heart J* 2009;157:125-131.**

**Study Question:** What is the relative safety of enoxaparin for percutaneous coronary intervention (PCI) compared with unfractionated heparin (UFH) in patients with reduced renal function?

**Methods:** In this subset analysis of the STEEPLE trial, patients undergoing elective PCI received a bolus of intravenous enoxaparin (0.5 or 0.75 mg/kg, or activated clotting time (ACT)-adjusted UFH, stratified by planned glycoprotein (GP) IIb/IIIa inhibitor use. The target ACT was 200-300 in patients treated with GP IIb/IIIa inhibitors and 300-350 seconds in patients treated without GP IIb/IIIa inhibitors. Renal impairment (creatinine clearance ≤60 ml/min) was present in 659 (19%) of the patients.

**Results:** Bleeding complications were more frequent in patients with renal dysfunction (major bleeding 2.7% vs. 1.5%, $p = 0.04$), whereas there was no difference in the incidence of death, nonfatal myocardial infarction, or urgent target vessel revascularization between patients with and without renal impairment (5.7% vs. 6.5%). Enoxaparin was associated with less major bleeding than UFH in patients with normal renal function (0.9% for enoxaparin 0.5 mg/kg or 1.0% for enoxaparin 0.75 mg/kg vs. 2.6% with UFH), and less major bleeding with impaired renal function (2.6% or 1.8% vs. 3.8%). There was no difference in minor bleeding or ischemic events with enoxaparin- or UFH-treated patients.

**Conclusions:** Single bolus enoxaparin was associated with similar ischemic events and a trend for less major bleeding compared with UFH in patients with renal impairment undergoing PCI.

**Perspective:** Enoxaparin use in patients with severe renal dysfunction is associated with increased bleeding events. In this subset analysis, severe renal dysfunction was present in only 1% of patients, and even the subset with moderate dysfunction was underpowered to detect differences in outcome between enoxaparin and UFH. It would be premature to assume safety or efficacy of enoxaparin for PCI in patients with renal dysfunction based on these data.

*Summary written by: Hitinder S. Gurm, MBBS, FACC*

# Noninvasive Cardiology

## Myocardial Blood Flow in Patients With Low-Flow, Low-Gradient Aortic Stenosis: Differences Between True and Pseudo-Severe Aortic Stenosis. Results From the Multicentre TOPAS (Truly or Pseudo-Severe Aortic Stenosis) Study

**Burwash IG, Lortie M, Pibarot P, et al.**
***Heart* 2008;94:1627-1633.**

**Study Question:** Do myocardial blood flow and myocardial flow reserve differ in low-flow, low-gradient aortic stenosis (AS) depending on whether there is underlying true-severe AS or pseudo-severe AS?

**Methods:** In 36 patients with low-flow, low-gradient AS, dynamic [$^{13}$N] ammonia positron emission tomography (PET) perfusion imaging was performed at rest (n = 36) and during dipyridamole stress (n = 20) to quantify myocardial blood flow and myocardial flow reserve. Dobutamine echocardiography was used to classify patients as true-severe AS (n = 18) or pseudo-severe (n = 18) based on the indexed projected effective orifice area (EOAI) at a normal flow rate of 250 ml/s ($EOAI_{proj}$ ≤ or >0.55 $cm^2/m^2$).

**Results:** Compared with healthy controls (n = 14), patients with low-flow, low-gradient AS had higher resting mean myocardial blood flow (0.83 ± 0.21 vs. 0.69 ± 0.09 ml/min/g, p = 0.001), reduced hyperemic myocardial blood flow (1.16 ± 0.31 vs. 2.71 ± 0.50 ml/min/g, p < 0.001), and impaired myocardial flow reserve (1.44 ± 0.44 vs. 4.00 ± 0.91, p < 0.001). Resting myocardial blood flow and myocardial flow reserve correlated with indices of AS severity in low-flow, low-gradient AS with the strongest relationship observed for $EOAI_{proj}$ ($r_s$ = -0.50, p = 0.002 and $r_s$ = 0.61, p = 0.004, respectively). Compared with pseudo-severe AS, true-severe AS had a trend to a higher resting myocardial blood flow, similar hyperemic blood flow, but a significantly smaller myocardial flow reserve (1.19 ± 0.26 vs. 1.76 ± 0.41, p = 0.003). A myocardial flow reserve <1.8 had an accuracy of 85% for distinguishing true-severe from pseudo-severe AS.

**Conclusions:** Low-flow, low-gradient AS is characterized by higher resting myocardial blood flow and reduced myocardial flow reserve that relates to the AS severity. The degree of myocardial flow reserve impairment differs between true-severe and pseudo-severe AS, and may be of value for distinguishing these entities.

**Perspective:** Patients with true-severe low-flow, low-gradient AS benefit from surgical aortic valve replacement. Dobutamine stress echocardiography traditionally is used to distinguish true-severe AS from pseudo-severe AS. On dobutamine infusion, left ventricular contractile augmentation with increased forward cardiac output results in higher gradients and persistent low valve area in patients with true AS, but an increase in valve area and no significant increase in gradients in patients with pseudo-AS. However, among some patients with severely decreased systolic function, or in others with concomitant coronary artery disease and inducible ischemia during dobutamine infusion, left ventricular contractility may not substantially improve. Since the therapeutic implications are substantial, using PET scanning to accurately distinguish patients with an equivocal response to dobutamine could have clinical implications in a subset of patients with low-flow, low-gradient AS of unclear nature.

*Summary written by: David S. Bach, MD, FACC*

# Prevention/Vascular

## Modulation of Blood Pressure by Central Melanocortinergic Pathways

**Greenfield JR, Miller JW, Keogh JM, et al.**
***N Engl J Med* 2009;360:44-52.**

**Study Question:** What is the association between central melanocortinergic signaling and blood pressure in overweight or obese subjects?

**Methods:** The authors compared blood pressure, heart rate, and urinary catecholamine levels in overweight or obese subjects with a loss-of-function mutation in the melanocortin 4 receptor (MC4R) versus equally overweight subjects with normal MC4R function. They also reported the response to the use of an MC4R agonist in 28 volunteer overweight or obese subjects.

JACC Vol. 53, No. 9, 2009
March 3, 2009:817–24

**Results:** Subjects with MC4R deficiency had markedly lower prevalence of hypertension (24% vs. 53%, p = 0.009). After exclusion of subjects taking antihypertensive medications, blood pressure levels were significantly lower in the MC4R-deficient subjects than in controls, with mean systolic blood pressure of 123 ± 14 versus 131 ± 12 mm Hg (p < 0.05). Diastolic blood pressure means were also significantly different; 73 ± 10 versus 79 ± 7 mm (p < 0.05). The authors also reported significant differences in increases in heart rate upon awakening (p = 0.007) and heart rate upon euglycemic hyperinsulinemia exposure (p < 0.001), with significantly lower heart rate in the MC4R-deficient subjects. Twenty-four hour urinary norepinephrine excretion was also significantly lower in the MC4R-deficient subjects (p < 0.05). Exposure to 1.0 mg of MC4R agonist in overweight or obese controls resulted in significant increases in systolic blood pressure (9.3 ± 1.9 mm Hg) and diastolic blood pressure (6.6 ± 1.1 mm Hg) compared with placebo (p < 0.001) after 24 hours. Differences in blood pressure were not explained by insulin levels.

**Conclusions:** These studies suggest melanocortinergic signaling is involved in the control of human blood pressure through an insulin-independent mechanism.

**Perspective:** An important area of research in hypertension could be the role of melanocortinergic signaling in the hypertensive response of the metabolic syndrome, or obesity-related hypertension. This may suggest opportunities for therapeutic intervention for hypertension and/or the hypertension associated with overweight/obesity. The metabolic syndrome is associated with increases in sympathetic activation, systemic inflammation, hypertension, and dyslipidemia. These data suggest that melanocortin may play an important role in the hypertension associated with obesity, and that this association may be independent of insulin. It is early, but this may be important to our understanding of the hypertension associated with metabolic syndrome—a significant and growing public health problem.

*Summary written by: James B. Froehlich, MD, FACC*

## Relationship Between Blood Pressure and Outdoor Temperature in a Large Sample of Elderly Individuals: The Three-City Study

**Alperovitch A, Lacombe JM, Hanon O, et al.**
***Arch Intern Med* 2009;169:75-80.**

**Study Question:** Is there a relationship between blood pressure and outdoor temperature in the elderly?

**Methods:** The authors presented data from the large Three-City Study (3C study), looking at the relationship between dementia and vascular disease in 8,801 subjects ≥65 years not living in an institution. Outdoor temperature was recorded at 11:00 a.m. each day. The authors investigated the relationship between variations in blood pressure and temperature at the time of baseline blood pressure measurement, as well as the blood pressure measurement at 2-year follow-up.

**Results:** Both systolic and diastolic blood pressure values varied across the seasons and across quintiles of outdoor temperature at the time of blood pressure measurement. Increasing temperature was associated with decreased systolic blood pressure, with an observed 8 mm Hg decrease between the lowest and highest outdoor temperature quintiles. Differences in blood pressure between baseline and follow-up were strongly related to outdoor temperature, such that higher temperature at follow-up was associated with a greater decrease in blood pressure.

**Conclusions:** Outdoor temperature and blood pressure correlated strongly in the elderly, especially in those ≥age 80. Periods of extreme temperatures should prompt careful monitoring of blood pressure and antihypertensive treatment in the elderly.

**Perspective:** This well-documented study suggests that either cold weather is associated with increases in blood pressure or warmer weather is associated with decreases in blood pressure, or both. This observation could have important implications for the assessment and treatment of hypertension in the elderly. The underlying mechanism of this difference is uncertain. Possibilities include differences in diet, hydration, sympathetic activity, or physical activity between higher and lower temperature seasons. Importantly, the investigators maintained a consistent ambient room temperature throughout this study, suggesting that outdoor weather conditions have an effect independent of the ambient temperature at the time of blood pressure measurement. Whatever the underlying mechanism, clinicians should consider the seasons and outdoor temperature—especially when practicing in climates that experience a large variation in seasonal temperature—when assessing the need for antihypertensive treatment.

*Summary written by: James B. Froehlich, MD, FACC*

*These journal article summaries were extracted from Cardiosource, your source for the best in cardiovascular information and education. www.cardiosource.com*